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Abstract: OBJECTIVE: During surgical clipping of intracranial aneurysms, reduction in SEP amplitude is thought to indicate cortical ischemia and subsequent neurological deficits. Since the sensitivity of SEP is questioned, we investigated SEP with respect to post-operative ischemia. METHODS: In 36 patients with 51 intracranial aneurysms, clinical evaluation and diffusion-weighted MRI (DWI) was performed before and within 24h after surgery. During surgery, time of temporary occlusion was recorded. MRI images were reviewed for signs of ischemia. RESULTS: For 43 clip applications (84%), we observed neither pathologic SEP events nor ischemia in MRI. In two cases where reduction lasted >10 min after clip release, SEP events correlated with ischemia in the MRI. Only one of the ischemic patients was symptomatic and developed a transient hemiparesis. CONCLUSIONS: While pathologic SEP events correlated with visible ischemia in MRI only in two cases with late SEP recovery, ischemia in MRI may have been transient or may not have reached detection threshold in the other cases, in agreement with the absence of permanent neurological deficits. SIGNIFICANCE: In complex aneurysm cases, where prolonged temporary occlusion is expected, SEP should be used to detect ischemia at a reversible stage to improve the safety of aneurysm clipping.

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MRI-validation of SEP monitoring for ischemic events during microsurgical clipping of intracranial aneurysms

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Abbreviations: SEP somatosensory evoked potential; MRI magnetic resonance imaging; DWI diffusion weighted MR-imaging

Highlights

- After aneurysm clipping, ischemia may appear in MRI without concomitant neurological deficits.
- Ischemia may appear outside the path monitored by SEP.
- SEP should be used in particular if prolonged temporary occlusion is expected.

Abstract

Objective: During surgical clipping of intracranial aneurysms, reduction in SEP amplitude is thought to indicate cortical ischemia and subsequent neurological deficits. Since the sensitivity of SEP is questioned, we investigated SEP with respect to postoperative ischemia.

Methods: In 36 patients with 51 intracranial aneurysms, clinical evaluation and diffusion-weighted MRI (DWI) was performed before and within 24 hours after surgery. During surgery, time of temporary occlusion was recorded. MRI images were reviewed for signs of ischemia.

Results: For 43 clip applications (84%), we observed neither pathologic SEP events nor ischemia in MRI. In two cases where reduction lasted >10 min after clip release, SEP events correlated with ischemia in the MRI. Only one of the ischemic patients was symptomatic and developed a transient hemiparesis.

Conclusions: While pathologic SEP events correlated with visible ischemia in MRI only in two cases with late SEP recovery, ischemia in MRI may have been transient or may not have reached detection threshold in the other cases, in agreement with the absence of permanent neurological deficits.

Significance: In complex aneurysm cases, where prolonged temporary occlusion is expected, SEP should be used to detect ischemia at a reversible stage to improve the safety of aneurysm clipping.

INTRODUCTION

Intraoperative neuromonitoring is used during neurosurgical procedures with the aim to detect brain dysfunction at a reversible stage to prevent irreversible lesions. During neurovascular surgical procedures, temporary occlusion of a parent artery is often mandatory for preparing the neck of the aneurysm sac. Even with short occlusion times, early detection of ischemic events is thought to be essential to prevent neurological deficits. The most common technique used clinically is intraoperative monitoring of somatosensory evoked potentials (SEP) where marked reduction of SEP amplitude is viewed as pathologic event which signals the possibility of ischemic brain damage (Friedman et al., 1987; Little et al., 1987; Martin et al., 2002; Mizoi and Yoshimoto, 1993; Schramm et al., 1990; Wiedemayer et al., 2004),

However, the occurrence of ischemic damage and subsequent neurological deficits is sometimes unpredictable from SEP, so that also the use of other techniques is reported (Calderon-Arnulphi et al., 2007; Neuloh and Schramm, 2004; Wess et al., 2010). Also, the occurrence of ischemic damage does not necessarily entrain subsequent neurological deficits (Krayenbühl et al., 2009) and many of the observed neurological deficits are only transient. Therefore the usefulness of intraoperative SEP during vascular surgery is not generally agreed on such that some centres rarely apply SEP in aneurysm surgeries, while others routinely apply SEP in most aneurysm surgeries.

As a new approach to investigate the prognostic value of SEP in aneurysm surgeries, we have obtained MRI-scans before and after surgery. Diffusion-weighted MRI (DWI) represents the gold standard for the detection of cerebral ischemia (Muir et al., 2006; Totaro et al., 2010) and allows the detection of silent ischemic lesions, which may produce SEP changes without neurological deficits. The general occurrence of ischemia in this patient group has been published earlier (Krayenbühl et al., 2009). While most studies on SEP evaluate neurological deficits after surgery, the present study correlates pathologic SEP events with the occurrence of ischemic lesions as detected by MRI-scans.

PATIENTS AND METHODS

Patients

For this study we enrolled patients with ruptured and unruptured intracranial aneurysms admitted between December 2005 and March 2007 to the department of Neurosurgery, University of Arkansas for Medical Sciences, who obtained a MRI-scan before and within 24h after microsurgical clipping of the aneurysm performed by the senior author (AFK). Patients with cerebral angiography after the initial MRI, patients who were not cooperative or had contraindications for MRI due to their medical condition and patients in whom emergency operation did not allow a MRI study before surgery were excluded from the study.

Thirty-six patients with 51 intracranial aneurysms were enrolled in the study (32 women, 4 men, median age 56 years, range 32-71). Patient data including number, location and size of the aneurysms (small <7 mm, medium 7-12 mm, large 13-25 mm, giant >25 mm) and the Yaşargil grading score (Yaşargil, 1984), were prospectively collected and analyzed. Clinical outcome was assessed at discharge using the Glasgow outcome score (GOS). The classification and location of the aneurysms has been described earlier (Krayenbühl et al., 2009).

The number of temporary clips applied was counted and the maximal and total time of temporary occlusion recorded. Also the total number of final clips applied was counted, including all the final clips that were put, removed or readjusted (only counted if the clip was completely opened) during the clipping process.

All patients or their first relatives were informed about the recordings and supplied written informed consent to the performance of the recordings and the subsequent publication of the data in anonymised form.

MRI-scans

The size and location of the aneurysms were analyzed. MR imaging included T1, T2, FLAIR, Perfusion and diffusion-weighted (DWI) sequences

before and within 24 hours after the surgical procedure. All MRI-scans were evaluated by one neuroradiologist (E.E.) for detection of signs of ischemia.

Surgical technique

Anesthesia was maintained intravenously (total intravenous anaesthesia, TIVA) with Remifentanil and Propofol, which is known to have the smallest effect on SEP (Samra et al., 2001). After obtaining the required depth of anaesthesia, the patient was positioned on the operating table and the head fixed in the Mayfield holder. Then subcutaneous needle electrodes were placed for intraoperative neuromonitoring before starting the skin incision.

For aneurysms in the anterior circulation - except for paraclinoid aneurysms - a classical pterional approach described by Yasargil with interfascial dissection of the temporal muscle and extensive drilling of the lateral sphenoid wing was used (Yaşargil, 1984). For paraclinoid aneurysms we used the pretemporal approach and for aneurysms of the basilar artery tip area its transcavernous extension as described in previous publications (Krisht and Kadri, 2005). Early cerebrospinal fluid (CSF) draining was performed by opening of the carotid cistern. In the extradural part of the pretemporal approach CSF was early released by a small opening of the dura over the Sylvain fissure incising the arachnoid membrane and by opening Meckel's cave after dissection of the temporal dura propria off the lateral wall of the cavernous sinus. The proximal Sylvain fissure and the anterior Sylvain fossa were then widely opened without the use of a retractor but with the help of soft pledgets as advocated by Yaşargil (Yasargil et al., 2010). The dissection of the Sylvain fissure and the anterior Sylvain fossa from distal to proximal using the "inside to outside" technique proposed by Yaşargil allows protection of the pial plane. The coagulation of any cortical vein was avoided when ever possible during this procedure. A brain retractor was only used during the clipping procedure allowing increased light and better visualisation. Short temporary clipping with subsequent coagulation and shaping of the aneurysm was routinely performed. No burst suppression was

performed nor was Mannitol or other medications used for brain protection during the clipping process.

Intraoperative Neuromonitoring

Stimulation of the median nerve and recording SEP signals was performed using the Endeavor CR IOM system (www.viasyshealthcare.com) for intraoperative monitoring. The acquisition time for one averaged SEP curve ranged 40-90 sec. Recordings were performed continuously after opening of the dura until closing of the dura.

To elicit SEP in case of MCA surgery, the median nerve was stimulated by needle electrodes at the wrist of the patients contralateral to the site of surgery. In the case of ACA or AcomA surgery, SEP was elicited by stimulating the tibial nerve bilaterally at the ankle of patients.

We analyzed the SEP contralateral to stimulation. For median SEP, the negative peak recorded in electrode CP3 of CP4 around 20ms after the stimulating pulse (N20) was analyzed to obtain the two observables latency and amplitude. For tibial SEP, latency and amplitude were derived from the positive peak in CPz around 40 ms after the stimulating pulse (P40). After induction and with anaesthesia in steady state, intraoperative baseline values were established and the recording parameters were maintained throughout the surgical procedure. In some patients, SEP amplitude faded due to prolonged anaesthesia (Kalkman et al., 1991; Rappaport et al., 1994) and the baseline was adapted. During the surgical intervention, SEP was monitored continuously.

The criterion of a pathologic event in the SEP was defined as either the reduction of amplitude below a threshold of 50% or the increase of latency by 10% (Toleikis, 2005). Furthermore, changes in SEP were considered reliable only if they were repeatable and sustained across at least two consecutive acquisitions. In case of pathologic event we checked for changes in anaesthesia or surgical events together with the surgeon. Whenever a pathologic SEP event was observed, the time interval to the previous clip placement was noted. After

clip release we documented the time of the SEP amplitude to recover to baseline.

Statistical Analysis

Statistical analysis included calculations of sensitivity and specificity of SEP during surgery, with radiological findings accepted as the gold standard. The outcomes from SEP and radiological examinations were dichotomised as normal/abnormal in order to calculate sensitivity and specificity. For MRI, signs of ischemia were defined as abnormal. For SEP, the occurrence of a pathological event was defined as abnormal. 95% confidence intervals were obtained using the binomial distribution and are presented in square brackets [ ]. All statistical analyses were done using Matlab R2010a (www.Mathworks.com).

RESULTS

During the treatment of the 51 aneurysms, only five patients (10% [3.3-21.4%]) showed pathologic events in the SEP. In all five patients SEP amplitude was attenuated, there was no instance SEP peak delay without amplitude attenuation. The durations of the pathologic events and their delay after clipping are listed in Table 1. The events occurred within 2-11 minutes (average 5 minutes 48 seconds) after applying the temporary clips. In all of these clippings, the SEP recovered back to baseline after an average of 10 minutes and 4 seconds. These clippings differed from the clippings without pathologic SEP events in that the number of final clips applied was larger ($p = 0.003$, Wilcoxon rank sum test).

Pathologic SEP events correlated with MRI-diagnosis of ischemia in the following two patients:

Pathologic SEP event in patient 4

A 47-year old female presented with subarachnoid haemorrhage Grade II with a large ruptured MCA bifurcation aneurysm on the right (Figure 1). She had

also a small unruptured MCA bifurcation aneurysm on the left side, which was treated later.

During temporary clipping a decrease in amplitude and latency was observed in the right cortical SEP response. Longest temporary occlusion time was 459 sec. SEP amplitude came back to baseline within 840 sec. Postoperatively the patient had no neurological deficits, but DWI showed an ischemic lesion in the caudate nucleus on the right side.

Pathologic SEP event in patient 5

A 32-year old female presented with subarachnoid haemorrhage Grade II with a giant ruptured basilar aneurysm (Figure 2). The aneurysm had bled also several years earlier, but was not treated then due to its dolichoectatic configuration. Intraoperative rupture occurred during dissection of the aneurysm, and maximal temporary occlusion time was 750 sec. SEP amplitude came back to baseline within 900 sec on the left and within 1800 sec on the right side after removal of the temporary clip. Postoperatively, the patient showed a transient left hemiparesis, which recovered within 3 days.

Validation of SEP monitoring against ischemia in MRI

To validate the prognostic value of SEP monitoring in our study, we have classified the instances of clip application for all 51 aneurysms with respect to diagnosis of ischemia in the MRI (Table 1). For 43 clippings, neither a pathologic SEP event nor ischemia in the MRI was observed (true negatives, 84% [71.4-93.0%]). In three cases, a pathologic SEP event was not followed by diagnosis of ischemia in the MRI (false positives, 6% [1.2-16.2%]). In three other cases, diagnosis of ischemia in the MRI was not preceded by a pathologic SEP event (false negatives, 6% [1.2-16.2%]). In the two cases described above (patients 4 and 5), pathologic SEP events correlated with diagnosis of ischemia in the MRI (true positives, 4% [0.5-13.5%]). In these two patients, time to recovery after clip release (840 sec for patient 4 and 1800 sec for patient 5, Table 1) was longest in

our patient group. Only one patient (patient 5, 2% [0.0-10.4%]) became symptomatic and developed a transient hemiparesis.

DISCUSSION

From a clinical perspective, SEP are recorded during aneurysm surgery to reduce the risk of perioperative ischemic brain damage and subsequent postoperative neurological deficits. Pathological events in the SEP are communicated to the surgeon to affect the surgical strategy (Wiedemayer et al., 2002). However, the relationship between pathological SEP events, ischemic damage and neurological deficits is not at all clear. For example, silent ischemia without neurological deficits may occur (Krayenbühl et al., 2009). Furthermore, the occurrence of pathological SEP events in 5 of our patients without permanent deficits confirm the well documented finding that interoperative SEP attenuation is not tightly correlated with postoperative neurological deficits (Wiedemayer et al., 2004). We aimed to understand this discrepancy by choosing not the occurrence of neurological deficits but the occurrence of ischemic brain damage in Diffusion weighted MRI as the endpoint of our study.

In two cases (patients 4 and 5), a pathologic SEP event was indeed followed by ischemia (true positives). In patient 5 ischemia was detected in right temporal cortex and in thalamus, a location that is within the pathway monitored by SEP. This patient showed neurological deficits postoperatively, albeit transient. Patients 4 and 5 stand out in that the time for the SEP amplitude to recover to baseline exceeded 10 min (Table 1). In three cases, ischemia occurred without prior SEP events (false negatives). However, ischemia occurred in the basal ganglia in patient 6, the internal capsule in patient 7 and the cerebellum in patient 8. These are small circumscribed lesions, which may explain why there was no postoperative neurological deficit detected. Since these locations are outside the monitored pathway they are also outside the scope of SEP monitoring. The cases are therefore excluded to determine the sensitivity, which then amounts to 100% in our study design (95% confidence intervals 15.8%-100.0%). The definition of false negative findings has to be accounted for

when comparing sensitivity with reports from the literature (Friedman and Curran, 1987; Little et al., 1987; Martin et al., 2002; Mizoi and Yoshimoto, 1993; Schramm et al., 1990; Wiedemayer et al., 2004).

In three other cases, pathologic SEP events did not entrain ischemia (false positives), leading to a specificity of 93% (95% confidence intervals 82.1%-98.6%). In these cases, ischemia may have remained below detection threshold in the MRI or may have been transient with a short recovery time. Furthermore, communication of the pathologic SEP event to the surgeon and the subsequent reaction may have prevented permanent ischemia, which is the primary goal of SEP monitoring.

The number of interventions where neither pathologic SEP events nor ischemia occurred was by far the largest (true negatives). The absence of pathologic SEP events was thus predictive of good collateral flow and the absence of post-operative symptomatic ischemia in 100% of patients and asymptomatic ischemia in 90% of patients.

CONCLUSIONS

Pathologic SEP events correlated with visible ischemia in the somatosensory pathway in two patients where the SEP amplitude attenuation lasted >10 min after clip release. In agreement with the absence of permanent neurological deficits, ischemia in MRI may have been transient or may not have reached detection threshold in the other cases. Especially in complex aneurysm cases, where prolonged temporary occlusion is expected, SEP should be used to detect ischemia at a reversible stage to improve the safety of aneurysm clipping.

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FIGURE CAPTIONS

Figure 1: Patient 4. Angiography and CT-Angiography showing a large MCA bifurcation aneurysm (A). Preoperative (B) and postoperative (C) DWI, with an ischemic lesion in the right caudate nucleus. SEP traces with a temporary decrease in amplitude (pathologic SEP event) (D).

Figure 2: Patient 5. Preoperative (A, B) and postoperative MRI (C, D) showing a thalamic infarction on the right side and a small cortical ischemia in a patient with a basilar aneurysm (E, F). SEP traces with begin and end (arrows) of interval of attenuated SEP amplitude (pathologic SEP event) (G).

Pat	Age	Delay of pathologic SEP event after temporal clipping		Duration of pathologic SEP event		Location of ischemia in MRI	Clips temp	Clips final	Occlusion total	Occlusion max temporary	Retraction total	Grade Yasargil	Location of Aneurysm	Aneurysm size	Neurolog. deficit
		left (sec)	right (sec)	left (sec)	right (sec)				(sec)	(sec)	(sec)				
1	61	240	240	300	120	-	1	12	2200	300	10200	1a	BA tip	large	-
2	58	270	120	150	180	-	10	4	1800	340	7200	4	BA tip	small	-
3	68	180	180	540	540	-	7	13	406	93	1988	0a	paraclinoid li	medium	-
4	47	420	420	840	840	basal ganglia	9	18	1186	459	4982	2a	MCA bif re	large	-
5	32	660	660	900	1800	thalamus & cx temporal right	4	10	1196	723	10149	2a	BA tip fusiform	large	transient
6	45	-	-	-	-	basal ganglia	11	7	2331	390	12922	3a	Acom	medium	-
7	38	-	-	-	-	internal capsule	6	5	645	258	13060	0b	BA tip	medium	-
8	42	-	-	-	-	cerebellum	11	2	4680	1754	17400	0b	SCA r	giant	-

Table 1: Patients with pathologic SEP events (No 1-5) and/or ischemia detected in MRI (No 4-8).